Bipolar Androgen Therapy (BAT)

Unmask The Truth

Russ Hollyer, Gleason 9, T3c, N1MO HSPC patient

PCa is heterogenous and is usually comprised of four cell types:

(A) HSPC Androgen Sensitive: Relies on external DHT to live. These are easily treated by ADT.

(B) CRPC Androgen Sensitive: Relies on DHT to live but has upregulated and/or mutated ARs so that it is more efficient at collecting DHT.

(C) CRPC Androgen Sensitive: Relies on DHT to live but can produce it internally if needed. These cells might be able to convert adrenal androgens into DHT (DHEA, DHEAS, androstenedione delta 4).

(D) CRPC Androgen Insensitive: Does not need DHT to live. These cells are very difficult to control and can morph into NEPC and small cell varieties.

When we use ADT, the goal is to drive testosterone down as low as possible. This deprives (A) of “fuel”.

Initially this appears to be successful. Usually in the early stages of PCa most cancer cells are (A) and most of them die when androgens are withheld. We are HSPC.

However, as (A) are killed, (B) and (C) start to grow and (D) will make an appearance. Eventually, the cancer is comprised primarily of cells that can live in low androgen conditions (CRPC).

The change from HSPC to CRPC typically takes 1-4 years. When PCa is CRPC or beyond it becomes much harder to control. If you have CRPC you can use hormones to shift the population back to (A). Clinical trials are showing us that by using BAT most patients can restore their sensitivity to ARB/ARSIs.

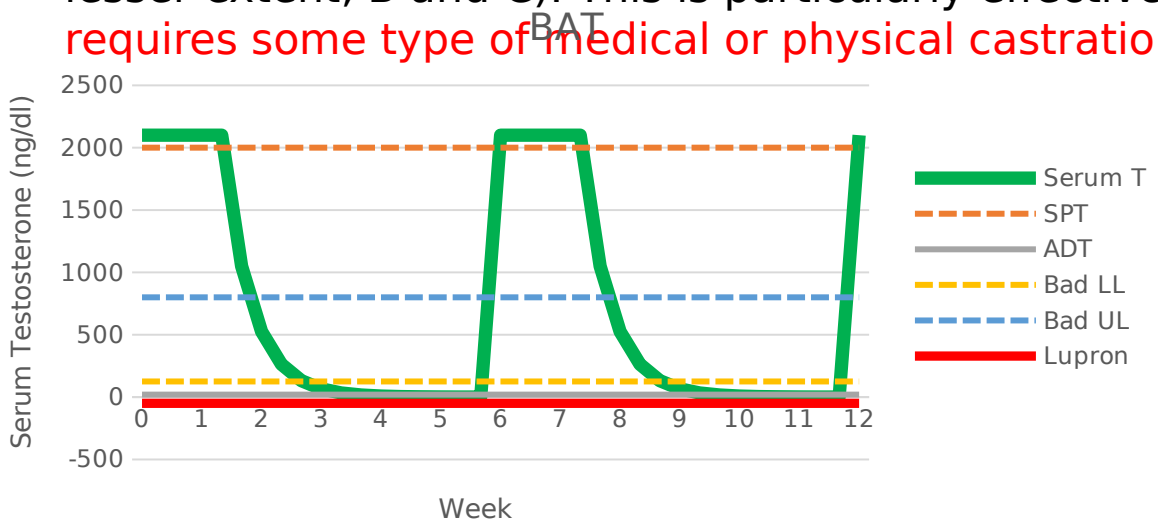
BAT has two parts

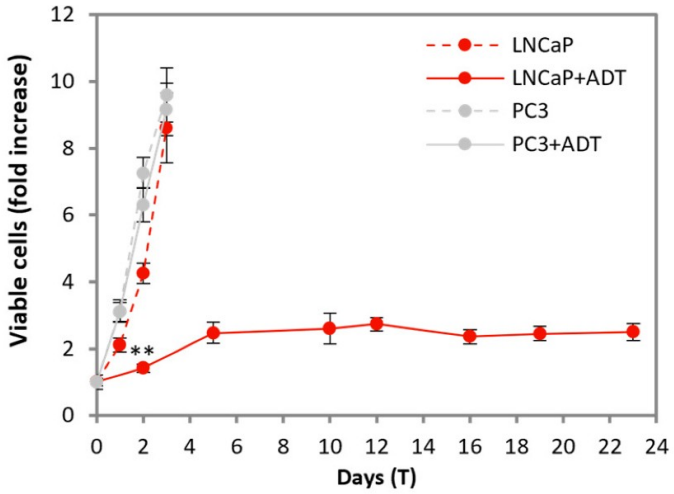
1. Rapidly increasing our androgens to a very high level (SPA). This increase makes the upregulated ARs of (B) a liability. Some of the mutations of (B) also become liabilities. SPA also induces DNA double strand breaks (DNA DSBs) and these serve to kill (A), (B), and (C).

If cancer cells are exposed to SPA for too long, (A) begins to dominate (they are dominant in HSPC men and present in smaller amounts in CRPC men).

Before this can happen, we move to part two.

2. Rapidly decrease our systemic androgens to a very low level (ADT). This environment controls cancer cells that require androgens for food (A and to a far lesser extent, B and C). This is particularly effective for HSPC men. Note that this requires some type of medical or physical castration.





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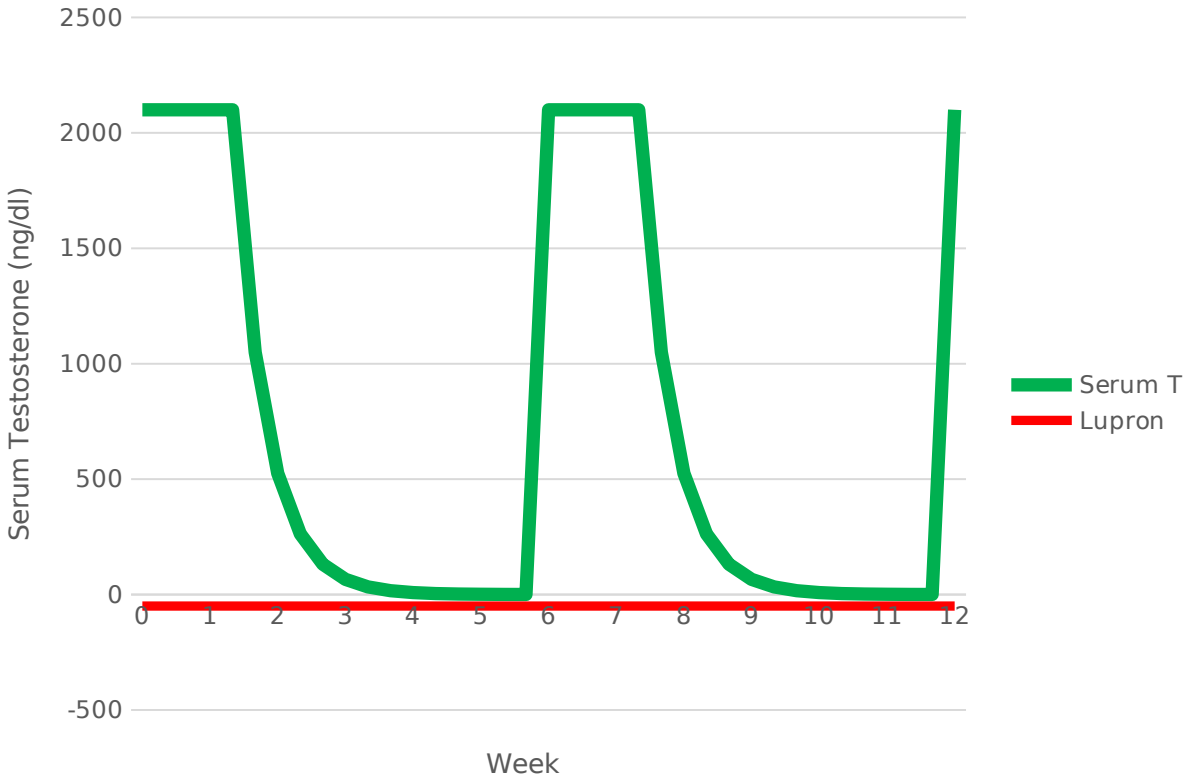
Drugs required:
Testosterone (propionate IM or Androgel are best)

If cancer cells are exposed to SPA for too long, (A) begins to dominate (they are dominant in HSPC men and present in smaller amounts in CRPC men). Before this can happen, we move to part two.

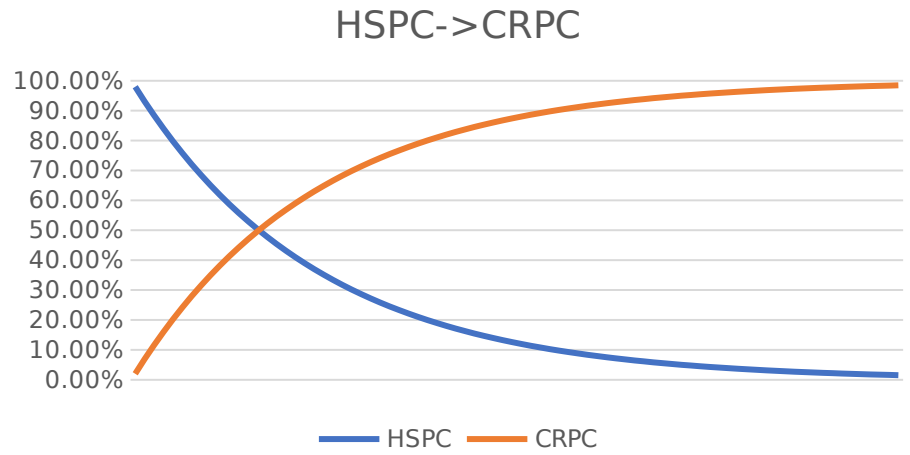
2. Rapidly decrease our systemic androgens to a very low level (ADT). This environment controls cancer cells that require androgens for food (A and to a far lesser extent, B and C). This is particularly effective for HSPC men. Note that this requires some type of medical or physical castration.

Drugs required:
Lupron or another form of ADT



HSPC vs. CRPC

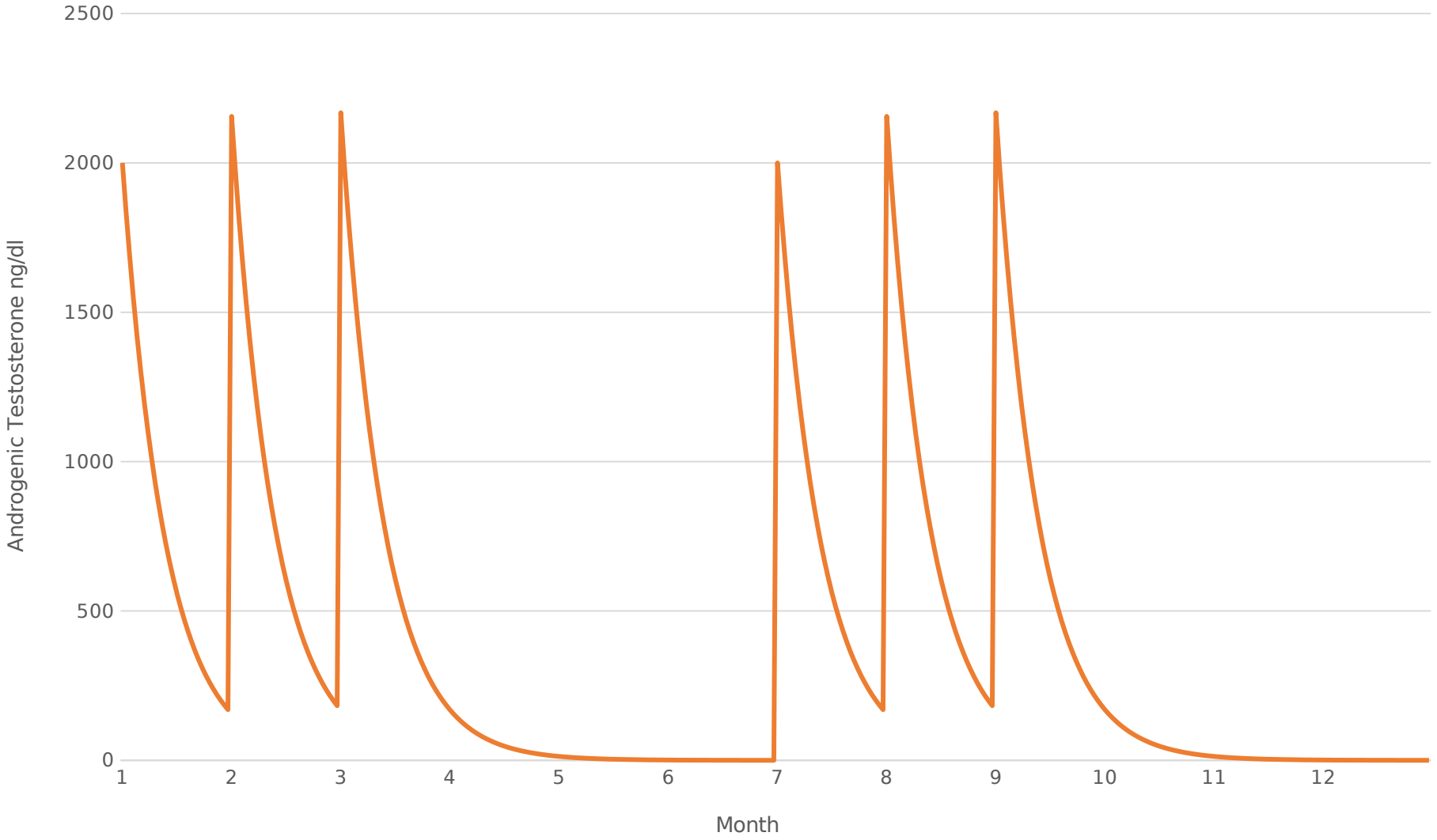
- SPA effectively inhibits growth of some CRPC cells (growth repression 3 days of 10 nM DHT 31-38%); cell/rat studies show that HSPC-like LNCaP cells are still inhibited in a dose dependent manner (growth repression 3 days of 10 nM DHT 21%). And some CRPC cells are not inhibited by SPA. HSPC appears to be “in the middle”.
- SPA mediated cell inhibition is greater in some CRPC cells than in HSPC cells but BAT consists of two phases. If a true castrate level is obtained in the second phase, inhibition is far greater in HSPC cells than in CRPC cells. Note: 4-week 400 mg cypionate cycles will never achieve true castrate levels.
- One of the known mechanisms of BAT is a down-regulation in ARs. However, BAT continues to work for many men. It appears that failure results, in part, when certain androgen insensitive cells appear. These are CRPC cells and not HSPC cells.
- I am HSPC. When I started BAT in 2021 my PSA was 0.17 and rising. After 16 months of BAT my PSA was 0.02. After 4 ½ years of BAT like maneuvers I am still HSPC.
- The HSPC -> CRPC transition is not digital. We do not know where the threshold of SPA repression lies. We need active ARs. HSPC cells have active ARs.



HSPC vs. CRPC continued

- If we can prevent HSPC -> CRPC progression, PCa might become a maintenance disease.
- The QoL benefits of SPA argue for its use even if it wasn’t as effective as ADT.
- The longer that ADT can be delayed, the better.
- Statements have been made that the BAT application to CRPC men in clinical trials was done because the bar to getting FDA SOC approval is lower. Other statements acknowledge that BAT might be effective for HSPC but that the primary focus for now is on CRPC.
- The BATMAN clinical trial was performed on HSPC men with very good results.
- A number of trials have been performed on CRPC men with decent to very good results.

BATMAN HSPC clinical trial



Candidates for BAT

- HSPC men.
- Early CRPC.
- Possibly middle or late CRPC with some conditions.

Disqualifiers:

- Symptomatic bone pain. You could make the pain worse.
- Bone mets that are close to the spine or are threatening a fracture. You could wind up with spinal cord compression or a fracture.
- If the prostate gland is bulky or a pelvic lymph node is close to obstructing your urinary tract, you could develop a renal obstruction or possibly even kidney failure.
- Genetic determinants of BAT response. The following mutation(s) have been displayed by extreme BAT responders:
  - BRCA2
  - TP53
  - TP53/BRCA2
  - TP53/ BARD1
  - BRCA2/ATM
  - ARID1A
  - ATM/RB1
  - CDK12 has some response.
  - CRPC men with homologous recombination repair (HRR) mutations had a 68% PSA response rate (any PSA reduction). Men without an HRR mutation had a 37% PSA response rate.
  - Men with tumor suppressor loss (TP53/PTEN, PTEN/RB1, TP53/RB1) exhibited a 54% PSA response rate.

Things to remember:

- If bone pain occurs, it is probably from inflammatory factors and not from cancer growth. Pain can be tested out using 300 mg of Androgel. If you have pain, Androgel will wash out in a few days.
- If muscle pain occurs, it can be reduced by using NSAIDs such as Ibuprofen or Aleve. You might need to use fairly high doses. Ibuprofen (Motrin) has a very short half-life so dosing might need to be done every 3 or 4 hours. Aleve has a much longer half-life, and you might find one or two doses a day will work.
- PSA might go up for a couple of months. This does not necessarily mean BAT is failing. Sometimes it takes time to work. Sometimes scans will be at odds with PSA. Always go with the scans. As Dr. Antonarakis mentioned, what makes it tricky is that sometimes PSA will increase for a couple of months and scans will

How I perform BAT

- Lupron continuously to reduce my body’s testosterone.
- Testosterone propionate injections to maintain an SPA level.

Optional:

- Continuously: Cabergoline to reduce prolactin.
- Continuously: Letrozole to reduce tumoral estrogen and estrogen converted from testosterone.
- SPT (phase 1): NPP injections on occasion for any joint issues.
- ADT (phase 2): SARMs such as Rad-140 during the ADT phase to maintain a weak anabolic environment.
- I sometimes introduce 1–2-day spikes of SPA. This can’t be done with cypionate. It is best accomplished with gels but can be done with propionate if darolutamide or another ARB/ARSI is used.
- Usually during ADT but sometimes during SPA: Occasional use of Zytiga and finasteride.
- ADT (phase 2): Estrogen patches (0.05-0.1 mg/day) to replace systemic estrogen.

- I am currently experimenting with olaparib to see how a short pulse performs with BAT.

Potential BAT synergists

- PARP inhibitors (e.g., Olaparib). Based on the DNA-DSB repair time, the half-life of Olaparib, the induction time of DNA-DSBs via SPA, Olaparib should be an effective synergist if started the day prior to a high T spike and continued for a total of 4 days. Clinical trial NCT03516812. Results show good synergism, but the results are not enhanced with BRCA or HRR mutations.

- Immunotherapy (e.g., Nivolumab). Clinical trial COMBAT-CRPC (NCT03554317). Good results.

- 2023: Carboplatin. Clinical trial HI-TECH (NCT03522064).

- 2024: BAT and darolutamide interleaved. Clinical Trial ExBAT (NCT04558866)

- 2026: BAT and Xtandi interleaved. Clinical Trial STEP-UP (NCT04363164). RESTORE and TRANSFORMER delved into the use of Xtandi for sequential therapy. STEP-UP will examine repeats and two different approaches.

- 2027: Radium-223. Clinical trial BAT-RAD (NCT04704505).

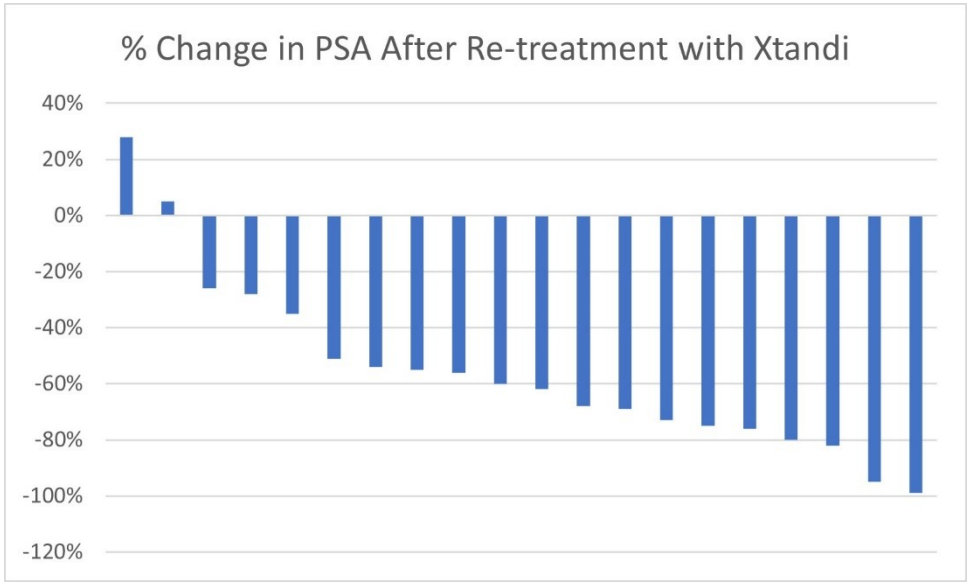
- I think that we may find that the following can be used:

    1. Zytiga for the first week or two following SPA. Washout and CYP17 restoration might take 4-6 weeks. I am not sure how Zytiga will interact with SPA. It might be prudent to restrict Zytiga use to every 3rd or 4th cycle.

    2. Extremely high testosterone pulses. Cell damage does not appear to level off at doses of R1881 that are roughly the equivalent of 50,000 ng/dl of testosterone. I tried out a 10k ng/dl pulse and my PSA dropped from 1.49 to 0.15 after I was castrate for a single day. The following month I tried a 25k ng/dl pulse. My PSA did not drop nearly as much, and I suspect that I damaged my immune system.

    3. Very short testosterone pulses. Most DNA damage occurs within hours of SPA application (certain genetic changes occur within minutes). DNA damage returns to baseline after 24 hours or so of application. HSPC cells apparently require higher and shorter SPA pulses. However, it has also been observed that exposure to an SPA environment increases the synthesis and decreases the turnover of cellular AR proteins.

Data from CRPC men in the RESTORE clinical trial
BAT was executed first. Regardless of whether it was useful as a monotherapy, men who had previously failed Xtandi were rechallenged with Xtandi.



TRANSFORMER showed us that **over 75% of CRPC patients who had failed Zytiga and were subsequently treated with BAT had a PSA50 response when treated with Xtandi. This was about 3 times the typical Xtandi post Zytiga failure response rate.**

Androgens

1. Increase sex drive
2. Increase muscle mass and strength
3. Improve memory and alleviate depression
4. Decrease fatigue
5. Increase bone mass
6. Increase hematocrit and RBC (this needs to be monitored)
7. Decrease systemic immune response. However, SPA increases immune factors in cancer cells.

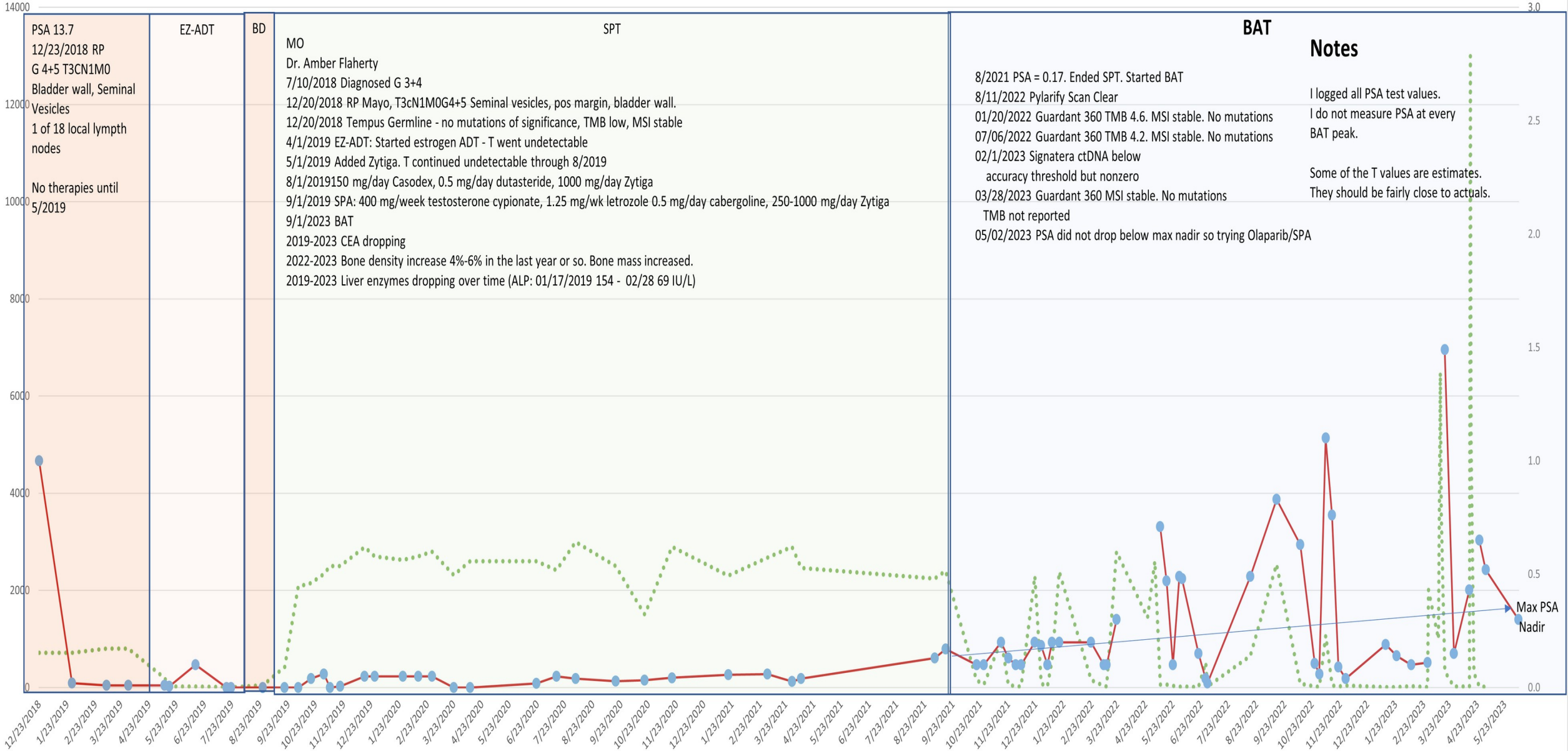
As of 5/17/2023

Time on BAT 613 days

Lean mass change 15.5 lbs.
Fat change -1.38%

Bone density change as of 8/2022: +5.20%. A separate test (DEXA-FIT) showed a 4.0% bone density increase as well as an overall bone mass increase of 4.8%.

ALP 126->80
ALT 26->17
AST 36->20
WBC 4.9->3.9
RBC 5.43->5.10


PSA 13.7
12/23/2018 RP
G 4+5 T3CN1M0
Bladder wall, Seminal Vesicles
1 of 18 local lymph nodes
No therapies until 5/2019
EZ-ADT
BD
SPT
MO
Dr. Amber Flaherty
7/10/2018 Diagnosed G 3+4
12/20/2018 RP Mayo, T3cN1M0G4+5 Seminal vesicles, pos margin, bladder wall.
12/20/2018 Tempus Germline - no mutations of significance, TMB low, MSI stable
4/1/2019 EZ-ADT: Started estrogen ADT - T went undetectable
5/1/2019 Added Zytiga. T continued undetectable through 8/2019
8/1/2019150 mg/day Casodex, 0.5 mg/day dutasteride, 1000 mg/day Zytiga
9/1/2019 SPA: 400 mg/week testosterone cypionate, 1.25 mg/wk letrozole 0.5 mg/day cabergoline, 250-1000 mg/day Zytiga
9/1/2023 BAT
2019-2023 CEA dropping
2022-2023 Bone density increase 4%-6% in the last year or so. Bone mass increased.
2019-2023 Liver enzymes dropping over time (ALP: 01/17/2019 154 - 02/28 69 IU/L)
BAT
8/2021 PSA = 0.17. Ended SPT. Started BAT
8/11/2022 Pylarify Scan Clear
01/20/2022 Guardant 360 TMB 4.6. MSI stable. No mutations
07/06/2022 Guardant 360 TMB 4.2. MSI stable. No mutations
02/1/2023 Signatera ctDNA below accuracy threshold but nonzero
03/28/2023 Guardant 360 MSI stable. No mutations
TMB not reported
05/02/2023 PSA did not drop below max nadir so trying Olaparib/SPA
Notes
I logged all PSA test values.
I do not measure PSA at every BAT peak.
Some of the T values are estimates. They should be fairly close to actuals.
Max PSA
Nadir
14000
12000
10000
8000
6000
4000
2000
0
3.0
2.5
2.0
1.5
1.0
0.5
0.0
12/23/2018
1/23/2019
2/23/2019
3/23/2019
4/23/2019
5/23/2019
6/23/2019
7/23/2019
8/23/2019
9/23/2019
10/23/2019
11/23/2019
12/23/2019
1/23/2020
2/23/2020
3/23/2020
4/23/2020
5/23/2020
6/23/2020
7/23/2020
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10/23/2020
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12/23/2020
1/23/2021
2/23/2021
3/23/2021
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6/23/2021
7/23/2021
8/23/2021
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10/23/2021
11/23/2021
12/23/2021
1/23/2022
2/23/2022
3/23/2022
4/23/2022
5/23/2022
6/23/2022
7/23/2022
8/23/2022
9/23/2022
10/23/2022
11/23/2022
12/23/2022
1/23/2023
2/23/2023
3/23/2023
4/23/2023
5/23/2023

BAT

8/2021 PSA = 0.17. Ended SPT.
Started BAT

8/11/2022 Pylarify
Scan Clear

01/20/2022 Guardant 360
TMB 4.6. MSI stable.
No mutations

07/06/2022 Guardant 360
TMB 4.2. MSI stable.
No mutations

02/1/2023 Signatera ctDNA below
accuracy threshold but nonzero

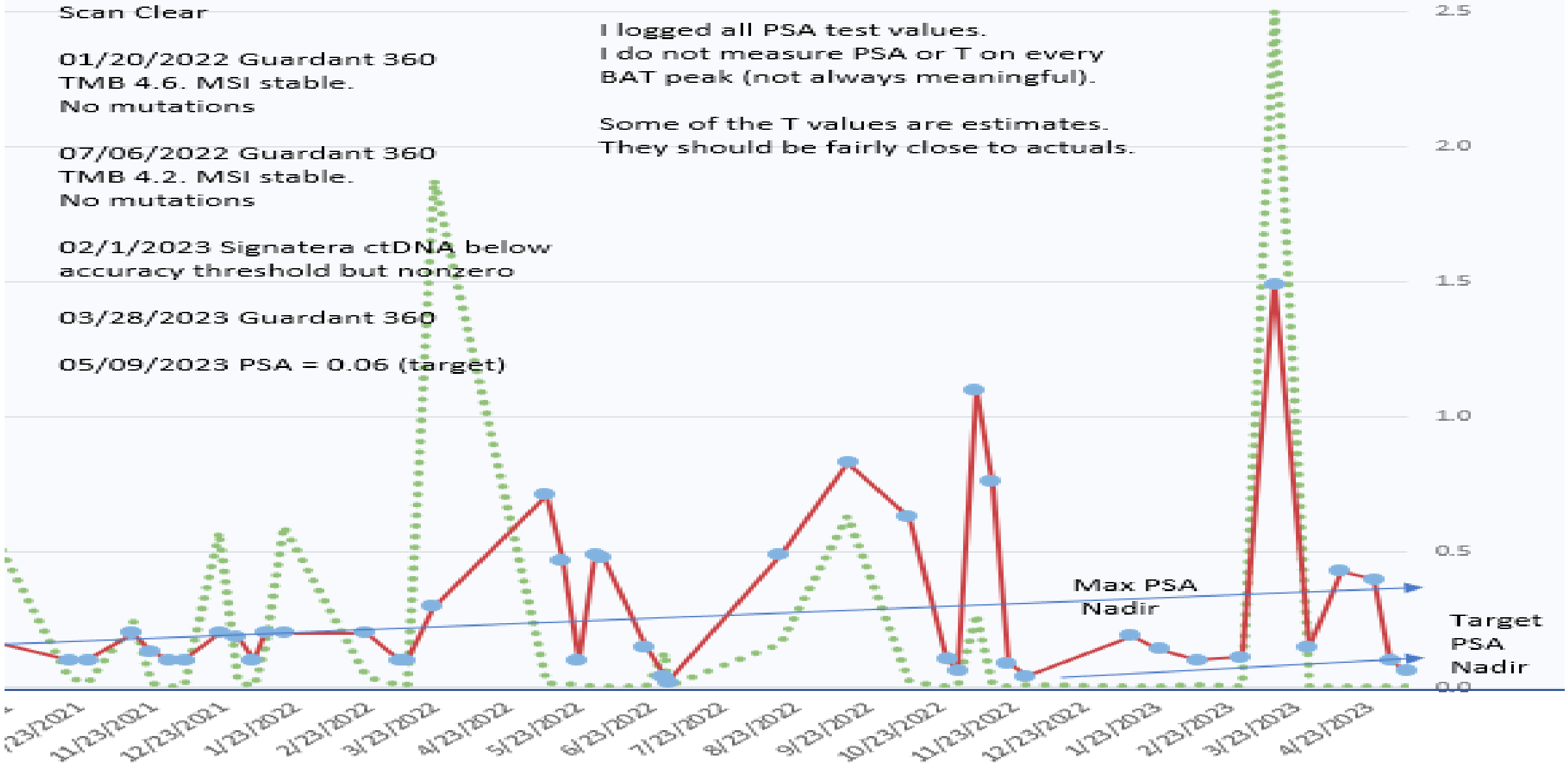
03/28/2023 Guardant 360

05/09/2023 PSA = 0.06 (target)

Notes

I logged all PSA test values.
I do not measure PSA or T on every
BAT peak (not always meaningful).

Some of the T values are estimates.
They should be fairly close to actuals.



Clinical trials:

1. **https://clinicaltrials.gov/ct2/show/NCT03734653**
2. **https://clinicaltrials.gov/ct2/show/NCT03554317**
3. **https://clinicaltrials.gov/ct2/show/NCT02090114**
4. **https://clinicaltrials.gov/ct2/show/NCT03516812**
5. **https://clinicaltrials.gov/ct2/show/NCT02286921**
6. **https://pubmed.ncbi.nlm.nih.gov/35938545/ https://clinicaltrials.gov/ct2/show/NCT01750398 (HSPC)**
7. **https://clinicaltrials.gov/ct2/show/NCT01084759**
8. **https://clinicaltrials.gov/ct2/show/NCT04424654**
9. **https://clinicaltrials.gov/ct2/show/NCT00586898**
10. **https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2738932/ (NCT00006044)**
11. **https://clinicaltrials.gov/ct2/show/NCT04558866**
12. **https://clinicaltrials.gov/ct2/show/NCT04704505**

Not complete:

13. **https://clinicaltrials.gov/ct2/show/NCT04363164**
14. **https://clinicaltrials.gov/ct2/show/NCT05081193**
15. **https://clinicaltrials.gov/ct2/show/NCT03522064**
16. **https://clinicaltrials.gov/ct2/show/NCT05011383**

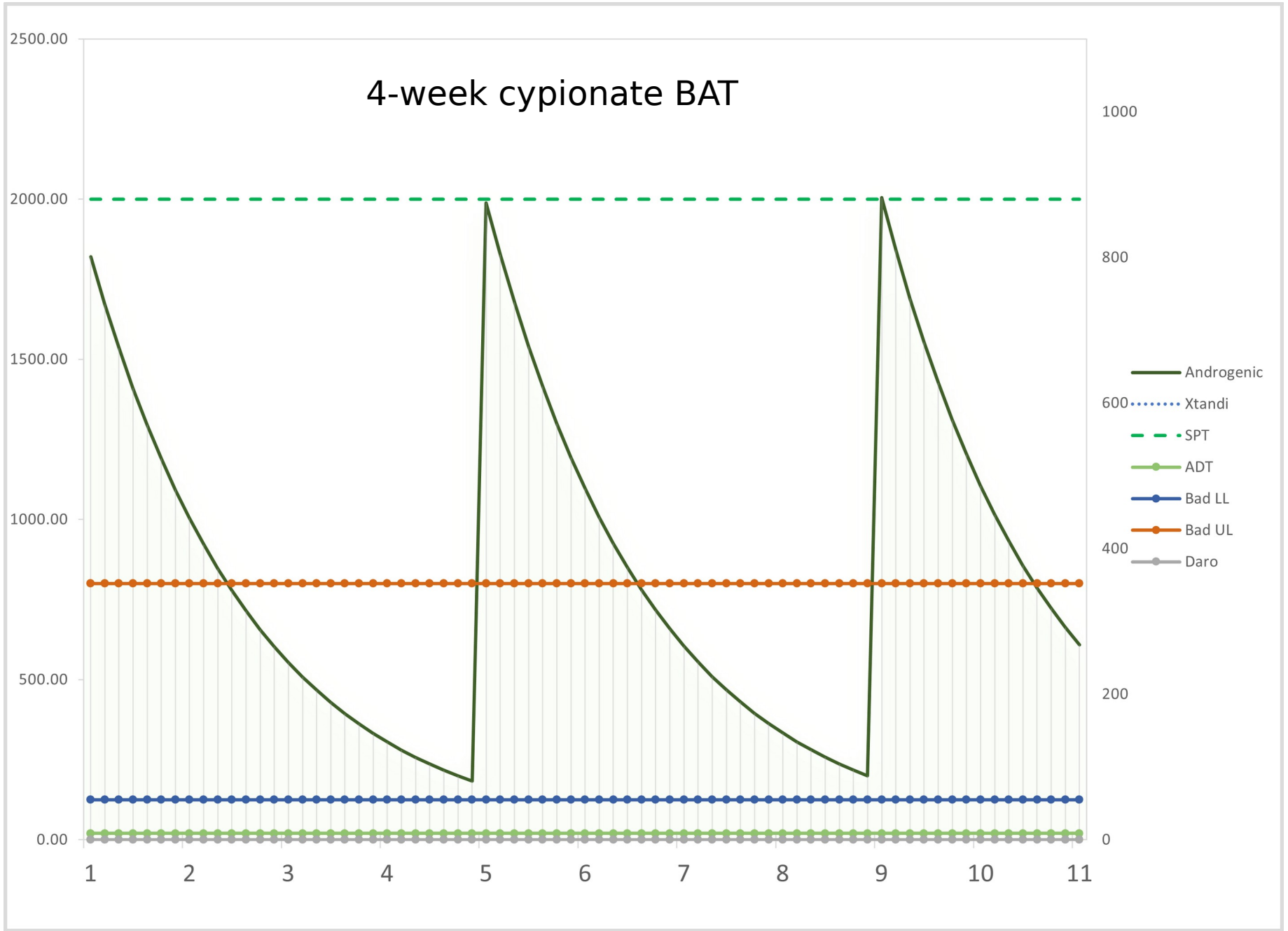
Study:

17. **https://aacrjournals.org/clincancerres/article/12/24/7414/193013/Rapid-Androgen-Cycling-as-Treatment-for-Patients**

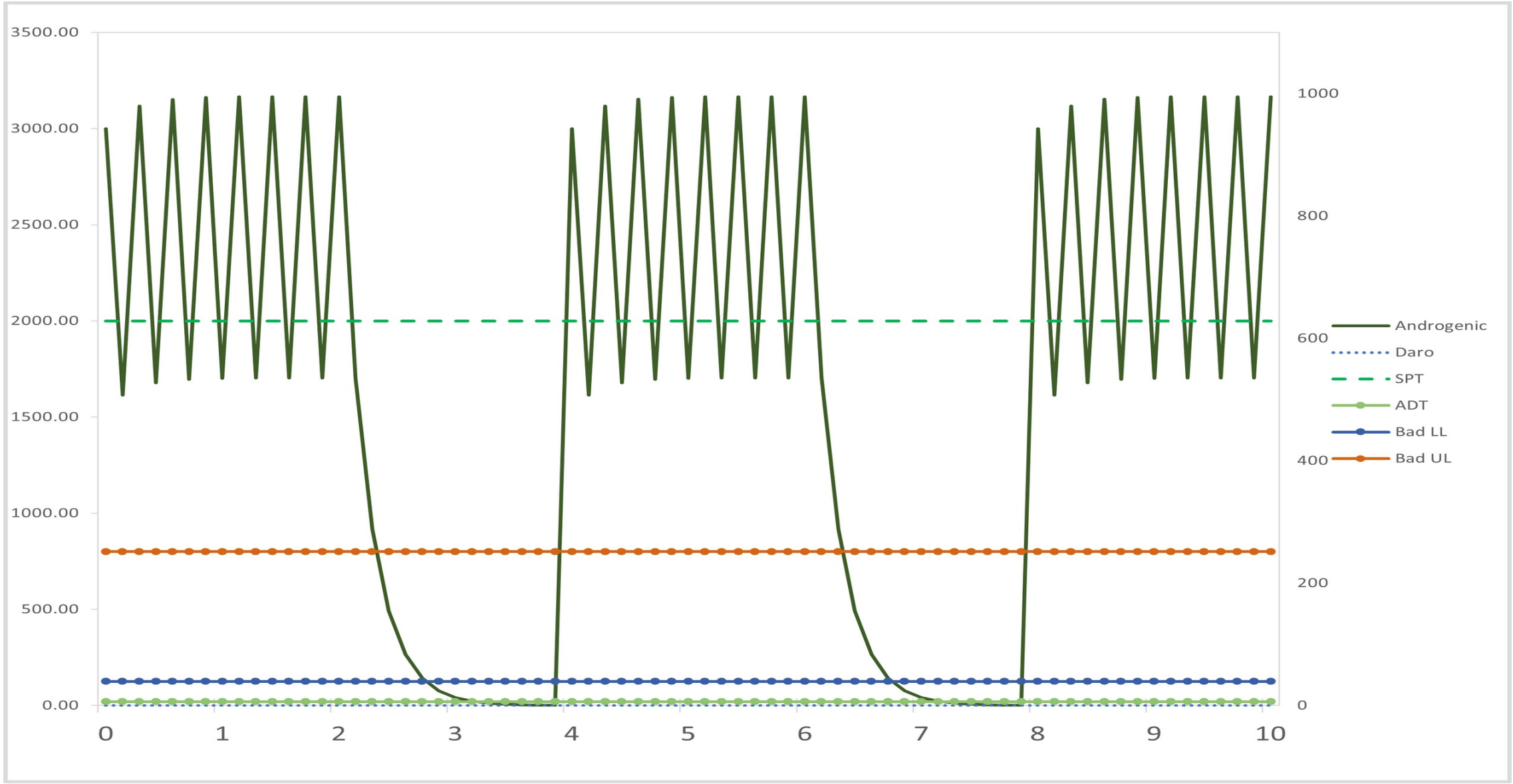
Bipolar androgen therapy (BAT): A patient's guide – PMC https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9313844/

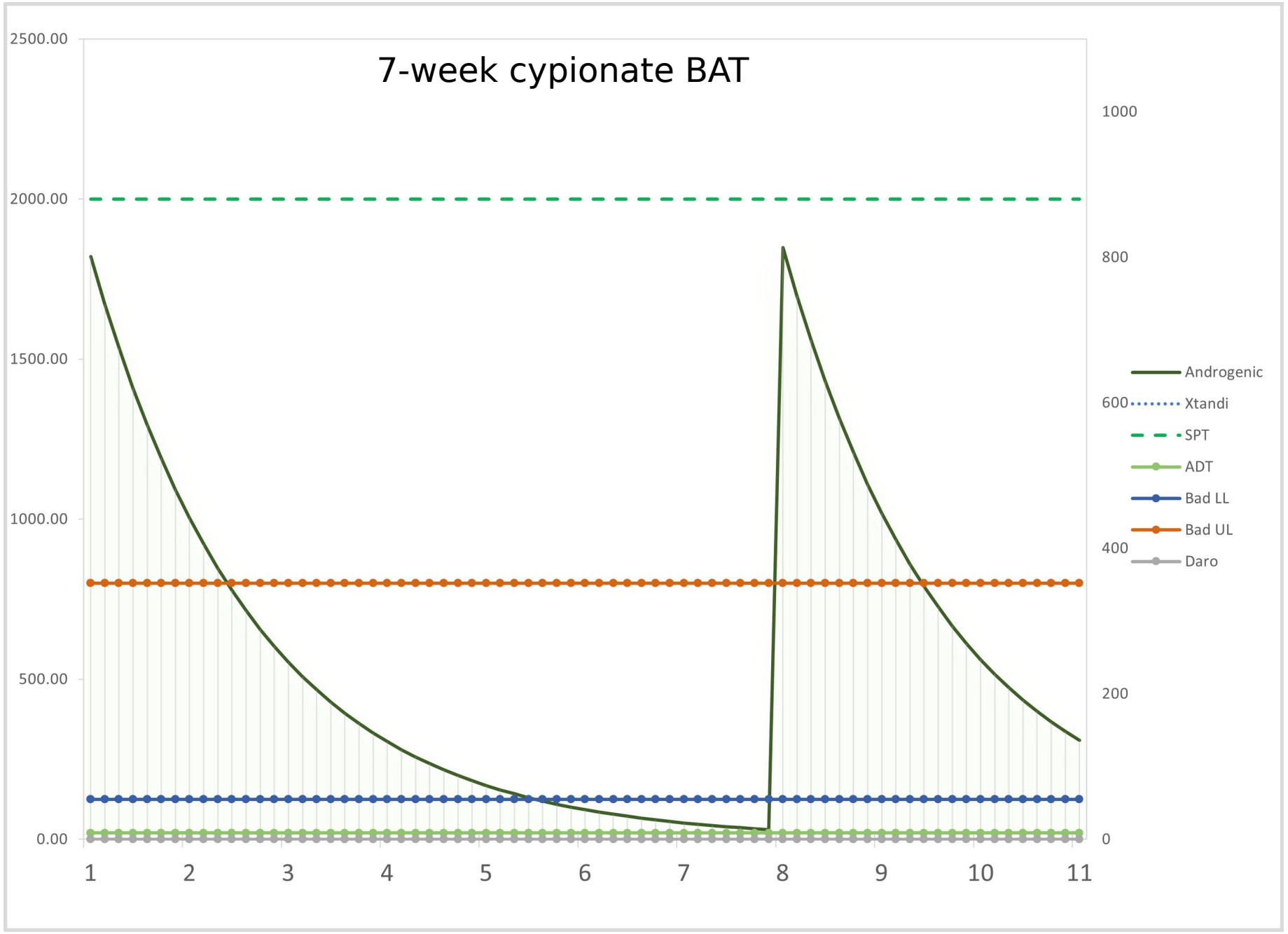
Dr. Sam Denmeade has volunteered to help MOs provide BAT to their patients. denmesa@jhmi.edu

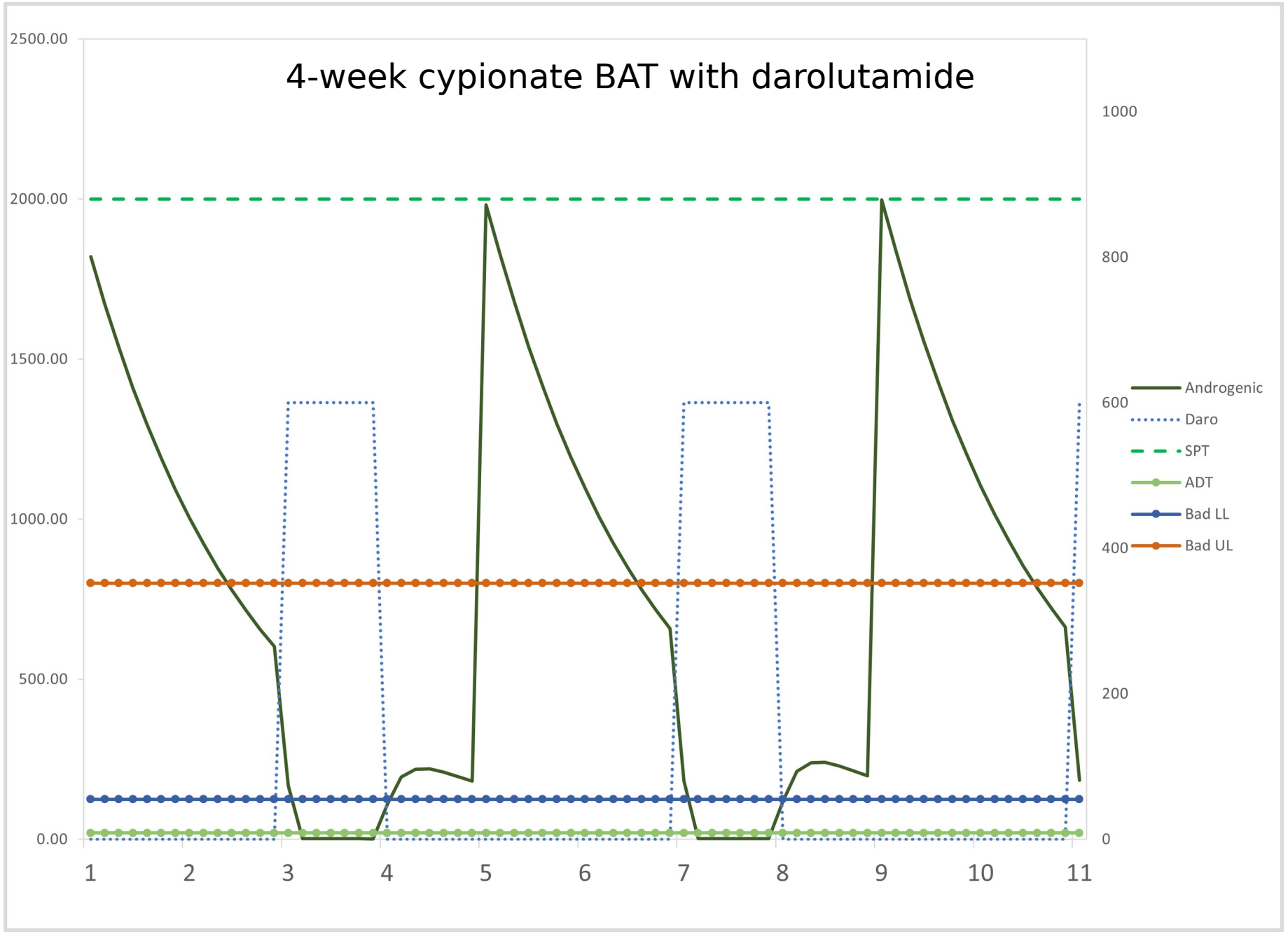
I'll help however I can. smurtaw59@gmail.com


4-week cypionate BAT
2500.00
2000.00
1500.00
1000.00
500.00
0.00
1000
800
600
400
200
0
1
2
3
4
5
6
7
8
9
10
11
Androgenic
Xtandi
SPT
ADT
Bad LL
Bad UL
Daro

4-week propionate BAT
AI continuously, tE2 replacement during the part of the 3rd and 4th week
You could also make this adaptive (using PSA)




7-week cypionate BAT
2500.00
2000.00
1500.00
1000.00
500.00
0.00
1000
800
600
400
200
0
1
2
3
4
5
6
7
8
9
10
11
Androgenic
Xtandi
SPT
ADT
Bad LL
Bad UL
Daro


4-week cypionate BAT with darolutamide
2500.00
2000.00
1500.00
1000.00
500.00
0.00
1000
800
600
400
200
0
1
2
3
4
5
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7
8
9
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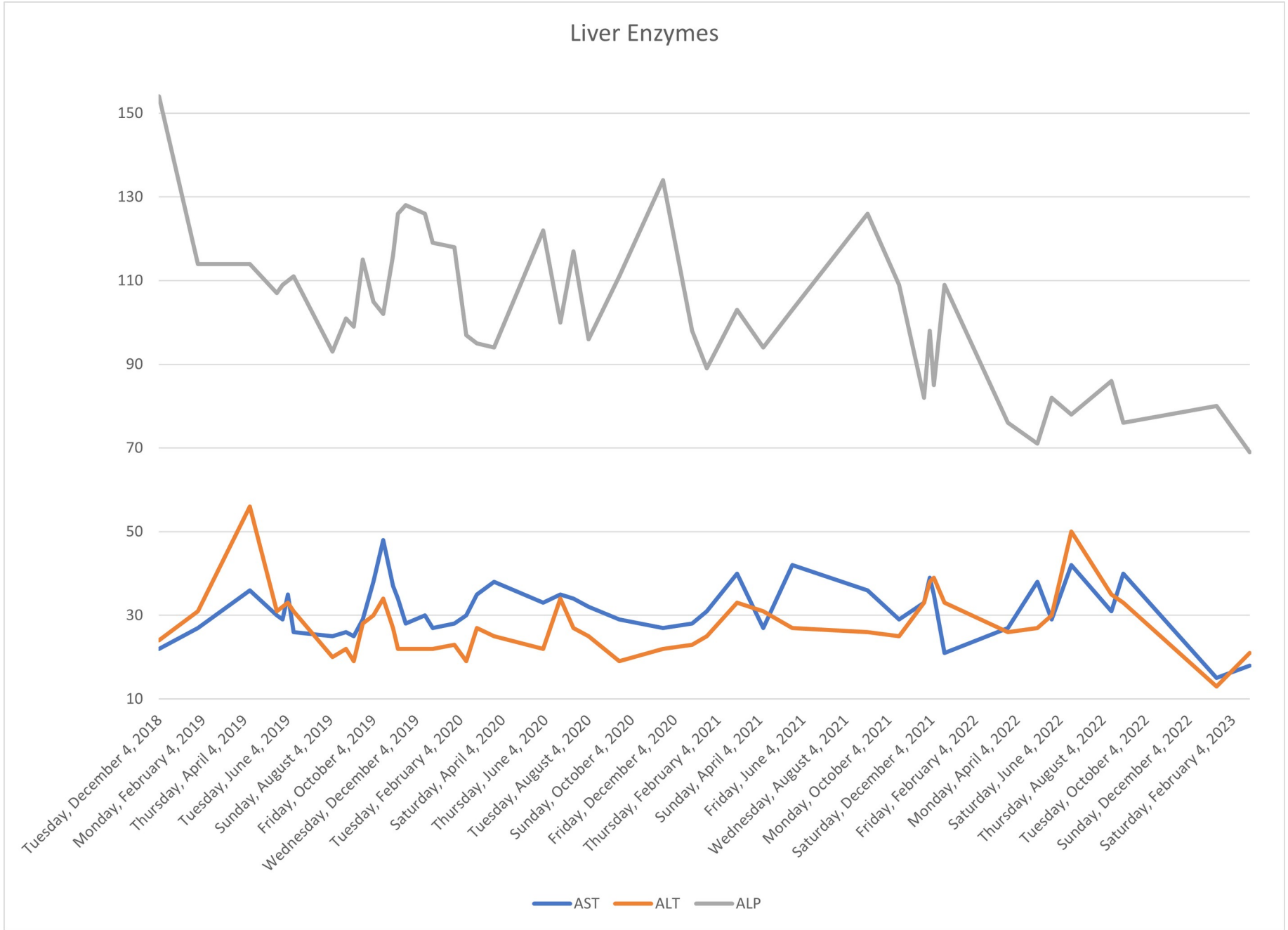
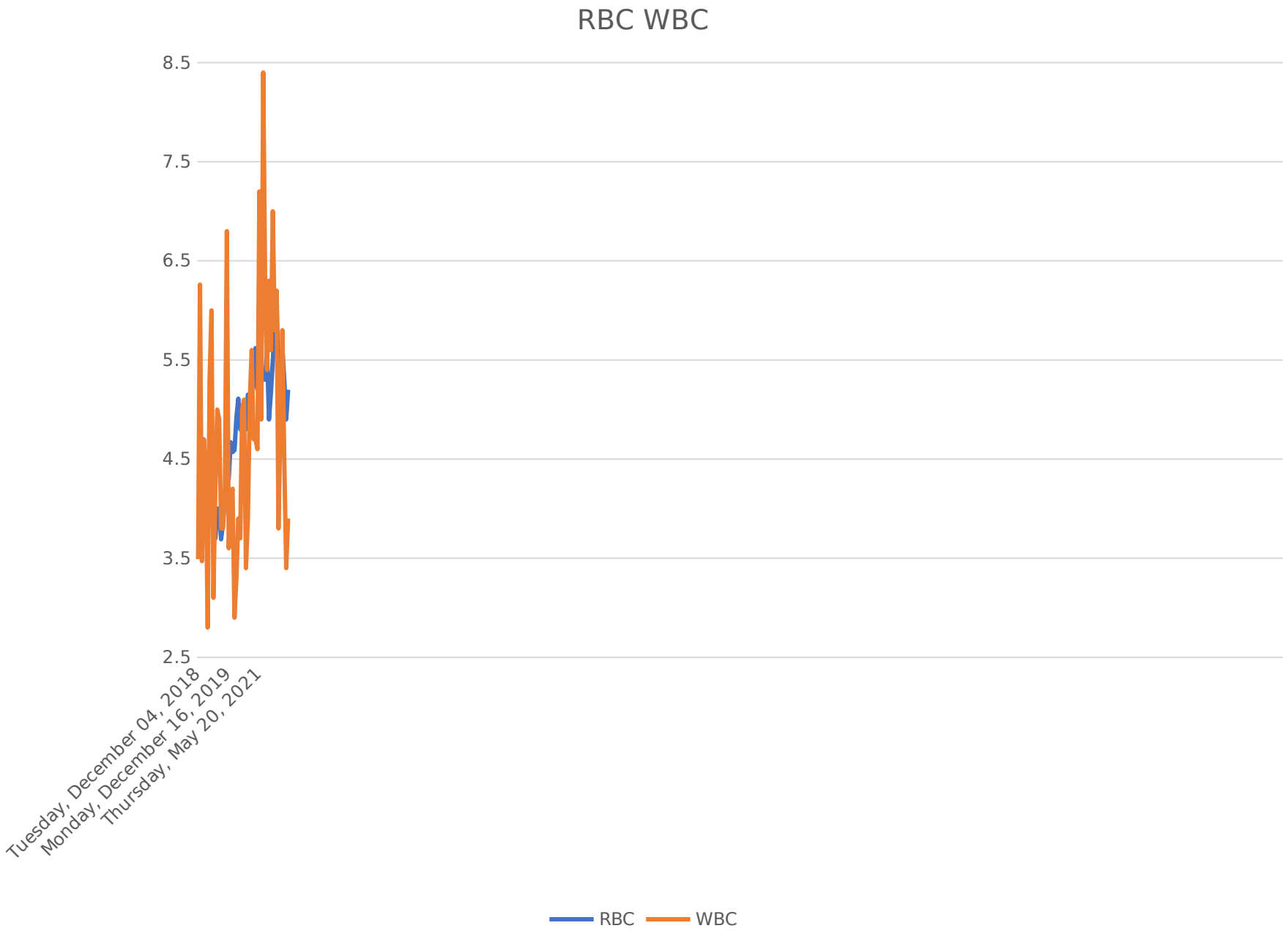
11
Androgenic
Daro
SPT
ADT
Bad LL
Bad UL


Liver Enzymes
150
130
110
90
70
50
30
10
Tuesday, December 4, 2018
Monday, February 4, 2019
Thursday, April 4, 2019
Tuesday, June 4, 2019
Sunday, August 4, 2019
Friday, October 4, 2019
Wednesday, December 4, 2019
Tuesday, February 4, 2020
Saturday, April 4, 2020
Thursday, June 4, 2020
Tuesday, August 4, 2020
Sunday, October 4, 2020
Friday, December 4, 2020
Thursday, February 4, 2021
Sunday, April 4, 2021
Friday, June 4, 2021
Wednesday, August 4, 2021
Monday, October 4, 2021
Saturday, December 4, 2021
Friday, February 4, 2022
Monday, April 4, 2022
Saturday, June 4, 2022
Thursday, August 4, 2022
Tuesday, October 4, 2022
Sunday, December 4, 2022
Saturday, February 4, 2023
AST
ALT
ALP


RBC WBC
8.5
7.5
6.5
5.5
4.5
3.5
2.5
Tuesday, December 04, 2018
Monday, December 16, 2019
Thursday, May 20, 2021
RBC
WBC